REMARKS

Amendments to The Specification

The title of this application has been amended to reflect the election of Species II (a), (irinotecan) in response to the Office Action mailed February 26, 2003.

The paragraph beginning on page 3, line 3 has been amended to correct a typographical error in the citation to the article Kuhn, J. G.,"Pharmacology of Irinotecan" *Oncology* (1998), **12** supp. 6, 39-42. The first citation to the Kuhn article is in the amended paragraph. Therefore, it is proper to give the full citation there. The full citation also appears at the paragraph beginning on p. 3, line 8 in the application as originally filed.

Status of The Claims

Claims 4-6, 8, 9, 13-30 and 51-79 were canceled without prejudice in Applicants' communication dated April 21, 2003 as directed to a non-elected invention. The Examiner has withdrawn claim 31 consistent with Applicants' election. Claims 1-3, 7, 10-12 and 32-50 are pending and under examination.

Claim 31 was objected to as dependent upon a canceled claim. Although claim 31 has been withdrawn from consideration, Applicants have also canceled claim 31 to obviate the objection.

Claims 36-39 were objected to as dependent upon a rejected base claim.

Claims 1-3, 7, 10-12, 32-35 and 40-50 stand rejected under 35 U.S.C. § 103(a) over the primary reference U.S. Patent Publication No. 2002/0136744 to McGlynn et al. ("McGlynn" or "the McGlynn publication") in view of Kuhn, J.K. "Pharmacology of Irinotecan" *Oncology* **1998**, *12*[8] Suppl. 6, 39-42 ("Kuhn").

Claims 1 and 7 have been amended in accordance with the Examiner's suggestion at an interview on December 10, 2003 to clarify that the gastric retention dosage form or liquid composition is retained in the stomach for a period of three hours or more. Support for the amendment can be found, *inter alia*, at page 23, lines 10 and 11 of the application.

Claim 34 has been amended to correct a spelling error.

Claim 40 has been canceled because it is a redundant claim in view of the current amendment of claim 7.

Claim 41 has been amended to change its dependency from canceled claim 40 to claim 7.

Claim 47 has been amended by substituting the term "irinotecan," which has antecedent basis in claim 7 from which it depends, for the term "antineoplastic agent" which no longer has antecedent basis in claim 7 after the amendments made in Applicants' communication dated April 21, 2003.

Interview Summary

Applicants thank the Examiner for the courtesy of an interview with their representative on December 10, 2003. At that interview, the relevance of the McGlynn reference was discussed. Applicants explained that, in their view, McGlynn does not teach or suggest to one skilled in the art to use irinotecan as a "beneficial agent" in the McGlynn dosage form. It is Applicant's understanding that the deficiency of McGlynn as a reference in this regard will be considered upon submission of the specific bases for it in this communication. Based upon an assumption that McGlynn does teach or suggest incorporating irinotecan in the McGlynn dosage form, the characteristics of the McGlynn dosage form were discussed. Applicants informed the Examiner that, according to their

understanding of the description of the McGlynn dosage form in the McGlynn publication, the McGlynn dosage form is not adapted to be retained in the stomach. The Examiner pointed out that, as shown in the McGlynn figures, some portion of a drug contained in the McGlynn dosage form would be released when the McGlynn dosage form passed through the patient's stomach, whether or not it was retained in the stomach. The Examiner suggested amending claim 1 to recite that the gastric retention dosage form or liquid composition of claim 1 is retained in the stomach for three hours or more. The accompanying remarks elaborate on Applicants' remarks at the interview.

The McGlynn Reference

McGlynn is directed to a drug delivery device for sustained delivery of a beneficial agent (drug) that has a pH dependent water solubility profile. The drug delivery device is particularly useful for drugs that are highly soluble in aqueous acid and poorly soluble in aqueous base. As stated in the McGlynn publication:

> The instant invention provides a means for administering, in a sustained-release manner up to about a 24 hour period, a therapeutic dose of a beneficial agent that has a water solubility profile that is highly dependent on pH levels in the environment of use.

(McGlynn ¶ [0027])

> This invention is particularly useful for beneficial agents which are very soluble at low pH values (less than about 2) and are practically insoluble at near neutral pH values (greater than or equal to about 5) ensuring a sustained release of the beneficial agent throughout all pH values.

(McGlynn ¶ [0027])

Such drugs tend to be released rapidly in the acidic environment of the stomach, which McGlynn calls "dose dumping." (McGlynn ¶¶ [0008][0032]) The McGlynn device is said to be "pH-insensitive" (McGlynn ¶¶ [0013], [0021], [0028]).

The McGlynn device addresses the problem of dose dumping by keeping the drug in a non-acidic local environment regardless of whether the device is in the stomach or intestine.

> Because the pH level in the core is near neutral, the beneficial agent remains insoluble and avoids the possibility of "dose dumping" in the stomach.

(McGlynn ¶ [0032])

The McGlynn device has a core surrounded by a coating made of water-insoluble, water-impermeable polymer. (McGlynn ¶ [0149]) The coating is perforated by one or more apertures. (McGlynn ¶ [0026]) The core contains a beneficial agent, a pH modulator and a water swellable polymer which upon hydration forms microscopic particles. (McGlynn ¶ [0021]-[0024]).

> Once the drug delivery device is within the environment of use, the water swellable polymer in the compressed core, which is exposed to the ambient aqueous solution at the coating apertures, begins to hydrate and produce gelatinous microscopic particles.

(McGlynn ¶ [0136]).

The microscopic particles produced on hydration and other core components form a gelatinous dispersion. (McGlynn ¶ [0136])

> The dispersion extrudes through the apertures of the device into the aqueous solvent, bringing the beneficial agent into the environment of use. In this novel device, the components of the compressed core move into the environment of use, carried along by the gelatinous microscopic particles, continually exposing new surfaces for further hydration and production of the dispersion.

McGlynn [0136]

According to the McGlynn publication, "[b]y 'gelatinous' is meant a *semisolid* system consisting of hydrated polymer interpenetrated by the aqueous solvent of the environment of use." (McGlynn ¶ [0137], emphasis added)

Irinotecan (CPT-11) is included in a long list of anti-neoplastic agents that can potentially be *co-administered* with the McGlynn device. (McGlynn ¶ [0167]). The McGlynn publication does not include irinotecan among the beneficial agents toward which the device is especially well adapted. Those beneficial agents are listed on pages 2-4 of McGlynn.

The § 103(a) Rejection

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P. § 2143 (8th ed, Feb. 2003 rev.)

According to the Office Action, "it would have been obvious to one of ordinary skill in the art at the time the invention was made to have expected the composition taught by McGlynn comprising irinotecan to have at least a portion of the released irinotecan converted into a metabolite before it is absorbed into the patient's bloodstream . . .." (Office Action p. 5, lines 4-6 from the bottom of the page)

To raise a *prima facie* case of obviousness, there must be some suggestion or motivation either in McGlynn, Kuhn or the knowledge generally available to one skilled in the art to select irinotecan as the "beneficial agent" in the McGlynn device. Applicants respectfully submit that Kuhn contains no suggestion to select irinotecan as the beneficial agent in the McGlynn device and such a selection is not within the knowledge generally available to the skilled artisan. Therefore, Applicants understand the § 103(a) rejection to be predicated upon some teaching in McGlynn to use irinotecan as the "beneficial agent" in the McGlynn device. However, McGlynn contains no such teaching. According to McGlynn, irinotecan is a drug that can be *co-administered* with the drug delivery device of the instant invention.

> The drug delivery device of the instant invention may also be ***co-administered*** with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the instant invention may also be ***co-administered*** with other well known cancer therapeutic agents that are selected for their particular usefulness against the condition that is being treated. Included in such combinations of therapeutic agents are combinations of a prenyl-protein transferase inhibitors and an antineoplastic agent. It is also understood that such a combination of antineoplastic agent and inhibitor of prenyl-protein transferase may be used in conjunction with other methods of treating cancer and/or tumors, including radiation therapy and surgery.

(McGlynn ¶ [0165])(emphasis added)

> Example classes of antineoplastic agents include, for example. . .. Particularly useful members of those classes include, for example, . . . CPT-11.

(McGlynn ¶ [0167])

The term "co-administration" allows for administering two drugs in separate dosage forms and that mode of co-administerration is clearly how one of ordinary skill in the art

would understand ¶ [0165] and ¶ [0167] of McGlynn. Therefore, these excerpts from McGlynn, upon which the Examiner appears to rely, do not teach or suggest to one skilled in the art to administer irinotecan as a "beneficial agent" in the core of the McGlynn drug delivery device.

When referring to specific compounds that can be used as "beneficial agents" McGlynn is clear. For instance, the McGlynn publications states:

> Additionally, ***the instant invention may also be useful for administering inhibitors of prenyl-protein transferase***, which may be used as radiation sensitizers, as described in WO 97/38697, published on Oct. 23, 1997, and herein incorporated by reference.

(McGlynn ¶ [0170])(emphasis added)

The McGlynn publication says that the McGlynn device is "useful" for "administering" the prenyl-protein transferase inhibitors of WO '697. In contrast, the McGlynn publication says the McGlynn device can be "co-administered with other well known therapeutic agents" like irinotecan. One skilled in the art reading the McGlynn publication would understand that the McGlynn device is especially adapted for administering the prenyl-protein transferase inhibitors of WO '697, but would not conclude that the McGlynn device was suited for adminstering irinotecan. Therefore, ¶ [165] and ¶ [167] of McGlynn do not teach or suggest to one skilled in the art to use irinotecan as a beneficial agent in the McGlynn device. Rather, their teaching is limited to the possibility of co-administration of the McGlynn device with irinotecan. This mere mention of irinotecan in the McGlynn publication would not motivate one skilled in the art to incorporate irinotecan into the McGlynn device.

The McGlynn publication states that the "term 'beneficial agent' broadly includes any drug or mixture thereof, that can be delivered from the system to produce a beneficial result." (McGlynn ¶ [0036) Applicants respectfully submit that defining the term "beneficial agent" in such a broad way is insufficient, in itself, to motivate one skilled in the art to select irinotecan as the beneficial agent in the McGlynn device from among "any drug or mixture thereof." *In re Jones* 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992) is relevant for the court's conclusion that a prior disclosure of a large genus does not make obvious the selection of a single species within the genus. That case involved a claim to the 2-(2'-aminoethoxy) ethanol salt of dicamba. A prior reference, Richter, disclosed that a genus of substituted ammonium salts of dicamba were useful as herbicides. Richter also disclosed certain structurally dissimilar dicamba ammonium salts but not the claimed 2-(2'-aminoethxy) ethanol salt of dicamba. The amine component of the claimed salt was known and disclosed in a second reference, Zorayan, where it was used as an additive in shampoo. The PTO Solicitor argued that "[t]he relative size of the genus disclosed by the prior art would not appear to be a controlling factor in determining whether a *prima facie* case of obviousness exists for a species encompassed within the described genus." *Id.* at 350. The Federal Circuit rejected that argument. After first concluding that there was no motivation in Zorayan to modify the structurally dissimilar dicamba ammonium salts to arrive at the 2-(2'-aminoethxy) ethanol salt of dicamba, the court then concluded "[n]or does the broad disclosure of Richter fill the gap . . .", summarily dismissing the solicitor's argument. *Id.* at 351. Likewise, in this instance the definition of "beneficial agent" in McGlynn as "any drug or mixture thereof" encompasses a very large genus of compounds. The large genus does not provide motivation to select irinotecan as a beneficial agent in the McGlynn device.

For the foregoing reasons, Applicants respectfully submit that there is no teaching or suggestion in the McGlynn publication that would motivate one skilled in the art to modify the McGlynn device by selecting irinotecan as the beneficial agent.

Assuming *arguendo* that there were motivation to modify McGlynn by selecting irinotecan as a beneficial agent, the combination of McGlynn and Kuhn still would not render Applicants' invention *prima facie* obvious. *Prima facie* obviousness based upon a combination of references requires that the references teach or suggest all the claim limitations. M.P.E.P. § 2143 (8th ed. Feb. 2003 rev.) Neither McGlynn nor Kuhn teaches or suggests a gastric retention solid dosage form or liquid composition containing irinotecan. The McGlynn publication is silent as to whether the McGlynn device effects gastric retention. Therefore, the Office bears the burden of providing a rationale or evidence tending to show that the McGlynn device would inherently be retained in the stomach. M.P.E.P. § 2112 (8th ed. Feb. 2003 rev.). The July 8, 2003 Office Action does not provide such rationale or evidence.

Moreover, the McGlynn publication suggests that the McGlynn device would not be retained in the stomach during ordinary use. One means of gastric retention taught by the present invention uses a hydrogel composition that swells in gastric fluid to a size that obstructs passage of the dosage form through the pylorus. Clearly, the McGlynn device is not designed to swell since swelling would require breakage of the water-impermeable polymer coating. Breakage of the water-impermeable polymer coating would allow drug release to circumvent the gel extrusion mechanism which enables sustained-release of the beneficial agent. (McGlynn ¶ [0032]). According to the McGlynn publication, extrusion of a dispersion through the apertures of the device brings the beneficial agent into the environment of use. (McGlynn ¶ [0136]) Therefore, breakage of the water-impermeable polymer coating, which

would expose more of the core to the environment of use, would accelerate release of the drug thereby rendering the McGlynn device unsuitable for its intended use as a sustained release drug delivery device. In addition, the gelatinous dispersion of microparticles extruded through the aperture(s) during operation of the McGlynn device as intended, does not appear capable of retaining the drug in the stomach since the dispersion is semi-solid according to the definition of "gelatinous" contained in the McGlynn publication (McGlynn ¶ 0137]) and is composed of "microparticles" whose sizes are measured in microns (McGlynn ¶ [0135]) making them individually able to pass through the pylorus.

For the foregoing reasons, Applicants respectfully submit that the rejection of claims 1-3, 7, 10-12, 32-35 and 40-50 for obviouness under § 103(a) is improper and the rejection should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that claims 1-3, 7, 10-12 and 32-50 are in condition for allowance. Early and favorable action by

the Examiner is earnestly solicited. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is urged to telephone the undersigned at the number below. The undersigned may also be contacted by email at pjohnson@kenyon.com.

Respectfully Submitted,

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